

8. CLAIMS APPENDIX

Claims on Appeal

1. (canceled)
2. The method of claim ¹~~55~~ wherein the mammal is human.
3. (canceled)
- 3 ~~4~~. The method of claim ¹~~55~~ wherein the anti-ErbB2 antibody is a growth inhibitory antibody effective to inhibit the growth of SK-BR-3 breast tumor cells *in vitro*.
- 4 ~~5~~. The method of claim ¹~~55~~ wherein the anti-ErbB2 antibody induces cell death when applied at an effective concentration *in vitro* to SK-BR-3 cells.
- 5 ~~6~~. The method of claim ¹~~55~~ wherein the anti-ErbB2 antibody induces apoptosis when applied at an effective concentration *in vitro* to SK-BR-3 cells.
7. (canceled)
- 6 ~~8~~. The method of claim ¹~~55~~ wherein the tumor is cancer.
- 7 ~~9~~. The method of claim ⁶~~8~~ wherein the cancer is selected from the group consisting of breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate and bladder cancer.
- 8 ~~10~~. The method of claim ⁷~~9~~ wherein the cancer is breast cancer.
- 9 ~~11~~. The method of claim ⁸~~10~~ wherein the breast cancer overexpresses ErbB2 at a 2+ level or more.
- 10 ~~12~~. The method of claim ⁹~~11~~ wherein the breast cancer overexpresses ErbB2 at a 3+ level.
- 11 ~~13~~. The method of claim ¹⁰~~12~~ wherein the breast cancer is a metastatic breast cancer.

¹⁰
12 ~~14~~. The method of claim ~~12~~ wherein the antibody has a biological characteristic of a 4D5 monoclonal antibody (ATCC CRL 10463) such that the antibody shows a growth inhibitory effect on SK-BR-3 cells in a manner that is dependent on the ErbB2 expression level and/or blocks binding of monoclonal antibody 4D5 to ErbB2.

¹²
13 ~~15~~. The method of claim ~~14~~ wherein the antibody binds essentially the same epitope as a 4D5 monoclonal antibody (ATCC CRL 10463).

¹²
14 ~~16~~. The method of claim ~~14~~ wherein the antibody is the monoclonal antibody 4D5 (ATCC CRL 10463).

¹²
15 ~~17~~. The method of claim ~~14~~ wherein the antibody is humanized.

¹⁵
16 ~~18~~. The method of claim ~~17~~ wherein the antibody is selected from the group consisting of humanized antibodies huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7 and huMAb4D5-8.

¹⁶
17 ~~19~~. The method of claim ~~18~~ wherein the antibody is humanized antibody huMAb4D5-8.

¹
18 ~~20~~. The method of claim ~~18~~ wherein the antibody is an ~~antibody fragment~~.

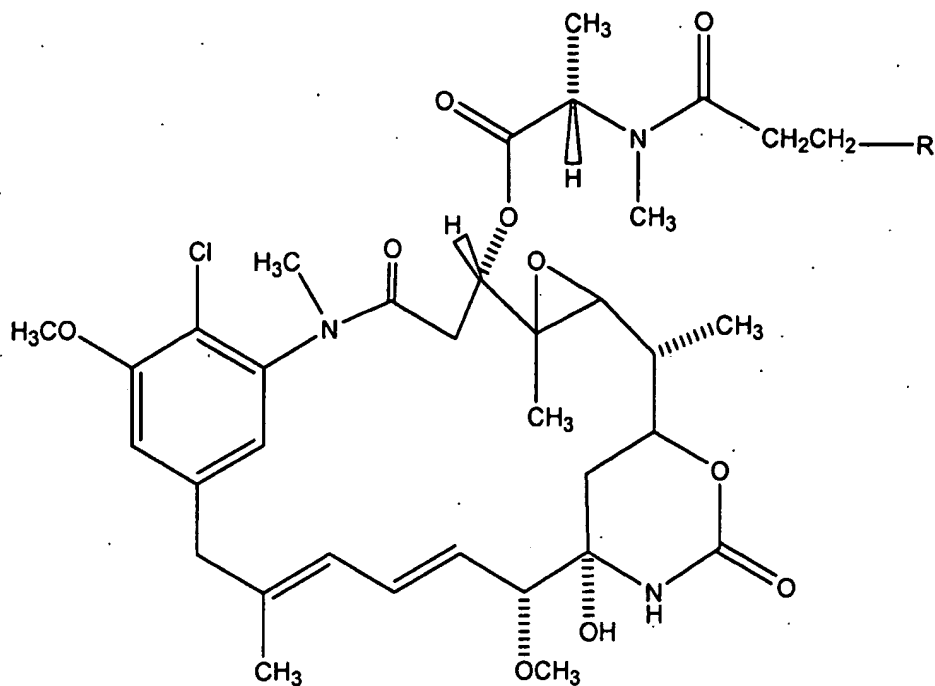
¹⁸
19 ~~21~~. The method of claim ~~20~~ wherein the ~~antibody~~ fragment is selected from the group consisting of a Fab, Fab', F(ab')₂, F_v fragment, diabody, linear antibody, and single-chain antibody molecule. *antigen binding fragment of said antibody*

22-23. (canceled)

¹
20 ~~24~~. The method of claim ~~25~~ wherein the maytansinoid is a maytansinol ester.

²⁰
21 ~~25~~. The method of claim ~~24~~ wherein the maytansinoid is a C-3 ester of maytansinol.

²¹
22 ~~26~~. The method of claim ~~25~~ wherein the maytansinoid is DM1 having the structure



wherein R is SH.

~~23~~ ²¹ The method of claim ~~55~~ wherein the antibody and maytansinoid are conjugated by a bispecific chemical linker.

~~24~~ ²³ The method of claim ~~27~~ wherein said chemical linker is N-succinimidyl-4-(2-pyridylthio)propanoate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) or N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP).

~~25~~ ²⁵ The method of claim ~~55~~ wherein the antibody and maytansinoid are conjugated by a linking group selected from the group consisting of a disulfide, thioether, acid labile, photolabile, peptidase labile, and esterase labile group.

~~26~~ ²⁵ The method of claim ~~29~~ wherein the linking group is a disulfide or a thioether group.

~~27~~ ²⁶ The method of claim ~~30~~ wherein the linking group comprises a disulfide group.

~~28~~ ~~32~~. The method of claim ~~55~~ wherein the conjugate comprises 1 to about 10 maytansinoid molecules per antibody molecule.

~~29~~ ~~33~~. The method of claim ~~32~~ wherein the conjugate comprises from about 3 to about 5 maytansinoid molecules per antibody molecule.

~~30~~ ~~34~~. The method of claim ~~55~~ further comprising the administration of a second antibody which binds ErbB2.

~~31~~ ~~35~~. The method of claim ~~34~~ wherein the second antibody comprises monoclonal antibody 2C4 or humanized 2C4.

~~32~~ ~~36~~. The method of claim ~~34~~ wherein the second antibody is humanized antibody, huMAb4D5-8.

~~33~~ ~~37~~. The method of claim ~~55~~ wherein treatment with the conjugate is followed by treatment with an unconjugated anti-ErbB antibody.

~~34~~ ~~38~~. The method of claim ~~32~~ wherein the conjugate is administered weekly at a dose of 0.1 to 10 mg/kg body weight.

~~35~~ ~~39~~. The method of claim ~~38~~ wherein said administration is followed by a dose of 0.3 mg/kg body weight approximately 10 weeks later.

~~36~~ ~~40~~. The method of claim ~~38~~ wherein the conjugate is administered weekly at a dose of 1 to 3 mg/kg body weight.

~~37~~ ~~41~~. The method of claim ~~40~~ wherein said administration is followed by a dose of 0.3 mg/kg body weight approximately 10 weeks later.

~~38~~ ~~42~~. The method of claim ~~55~~ wherein the conjugate is administered weekly at a dose of 0.1 to 5 mg/kg body weight for 4 to 6 weeks, followed by maintenance treatment with unconjugated anti-ErbB2 antibody.

- ³⁸
~~39~~ ~~43~~. The method of claim ~~42~~ wherein the unconjugated antibody is humanized antibody huMAb4D5-8 or humanized 2C4.
- ³⁰
~~40~~ ~~44~~. The method of claim ~~34~~ wherein said second antibody is conjugated with a cytotoxic agent.
- ⁴⁰
~~41~~ ~~45~~. The method of claim ~~44~~ wherein the cytotoxic agent is a maytansinoid.
- ¹
~~42~~ ~~46~~. The method of claim ~~55~~ wherein said treatment has an improved objective response rate compared to treatment with huMAb4D5-8 alone.
- ¹
~~43~~ ~~47~~. The method of claim ~~55~~ wherein said treatment has a longer duration of response than treatment with huMAb4D5-8 alone.
- ¹
~~44~~ ~~48~~. The method of claim ~~55~~ wherein said treatment results in increased survival of the mammal treated compared with treatment with huMAb4D5-8 alone.

49-54. (canceled)

¹ ~~55~~. A method for the treatment of a tumor in a mammal, comprising the steps of (i) identifying said tumor as being characterized by overexpression of an ErbB2 receptor and as being a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells, and (ii) administering to a mammal having said tumor a therapeutically effective amount of a conjugate of an anti-ErbB2 antibody which binds to the 4D5 epitope with a maytansinoid.